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CIRCULARS AND DESCRIPTIVE MATTER SENT ON APPLICATION.

THE PHILIPPINE

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HYDROPHOBIA IN THE PHILIPPINES.

By F. W. DUDLEY[1] and E. R. WHITMORE.[2]

The question of whether rabies does or does not occur either among the lower animals or man in the Philippines has been unanswered for a long time, and, while a number of medical men have been convinced that rabies is present in this Archipelago and considerable clinical evidence in favor of that belief has been collected, still several attempts to demonstrate scientifically its occurrence have failed; furthermore, several trials having for their end the keeping alive of a strain of "fixed virus" imported from Japan, have been unsuccessful, the virus either did not kill rabbits in Manila at all, or ceased to do so very soon after its importation. The question therefore arose as to whether the virus of rabies could continue in a viable condition in this locality.

One of us, as the result of an extensive clinical experience in these Islands, became firmly convinced that rabies does occur here, and read a paper on "The Prevalence of Hydrophobia in the Philippine Islands" at the meeting of the Philippine Islands Medical Association, February 28, 1907.[3] Up to that time Dudley had collected statistics of 158 deaths from hydrophobia in the human, and since then has received additional reports of 244 deaths, making a total of 402 reported human deaths from hydrophobia in the Philippines since about October 1, 1902. Thirty-one of the thirty-nine provinces in the Philippines, to which must be added the Island of Mindanao (Moro Province) and the district of Manila, have reported deaths from hydrophobia. Many of these reports so accurately describe rabies that they can hardly refer to any other disease.

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[1] Attending surgeon, St. Paul's Hospital, Manila.

[2] Major, Medical Corps, United States Army, detailed for civil duty to the Biological Laboratory, Bureau of Science. The laboratory work was done at the Biological Laboratory, Bureau of Science.

[3] Dudley, F. W. *Jour. Amer. Med. Asso.* (1908), 51, 2143.

However, none of these cases had been proved to be rabies. Accordingly, we decided to take up the study of the problem and determine, if possible, whether rabies actually does exist in this Archipelago. On April 1, 1910, we mailed a circular letter to all the physicians in the Philippines, asking them to send us the heads or brains of animals killed for, or dead of, suspected rabies; the material to be sent packed in ice, or in 50 per cent glycerine where ice was not available. We requested also that they report any cases of human rabies to us, so that if possible we might see the patients.

In response to this circular, Dr. Salvador Gomez, of Angeles, Pampanga Province, sent us the bodies of two dogs on April 16, 1910. These two animals had been bitten by a suspected rabid dog on March 22, and their owner, recognizing the danger of rabies, kept them tied from that date.[4]

One of these dogs became sick on April 10, the other on April 14. They refused to eat, saliva dribbled from their mouths, and they showed a tendency to snap and bite at everything. One of them escaped one day, and after running about bit two other dogs and a pig. On the following day another of the dogs escaped and attacked its mate, and the two animals fought viciously. The owner then killed both in the way usual among the natives, namely, by striking them over the head with a club. A few hours afterwards Doctor Gomez learned of the incident, secured the bodies and sent them to us.

The animals had been dead about forty-eight hours when we received them and no ice had been available for packing them for shipment. The skull of one (number 2) had been crushed by the blow that killed it, and the brain cavity was filled with a mass of blood clots, brain tissue, and bone fragments. We succeeded in demonstrating Negri bodies in the brain tissue of both of these animals; in the hippocampus and cerebral cortex of dog number 1 and in a piece of the cerebellum of dog number 2. The bodies stained rather faintly and it was difficult to bring out the "inner bodies" because of the length of time which had elapsed since the death of the animals and the beginning of putrefaction of the brain tissue.

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[4] The natives throughout the Islands understand that a dog bitten by another is likely to die, and that a person bitten by such a dog will probably die. So, when a dog is bitten it is always killed or tied up.

An emulsion of the brain tissue from each dog was injected intramuscularly into five rabbits. Rats were not available for inoculation. The brain tissue of dog number 2 killed all rabbits within eighteen hours, because of the contamination which was present. All rabbits inoculated with the emulsion of brain tissue from dog number 1 died within from fifteen to twenty days with the symptoms of rabies, and we were able to demonstrate Negri bodies and Lentz passage bodies in the brains of these rabbits.[5] (See Pl. I.) This strain of virus was carried through seven passages in rabbits between April 17 and July 9, and at the end of that time it regularly killed rabbits with typical rabies in nine days when inoculated subdurally. We did not attempt to demonstrate Negri bodies or Lentz passage bodies in the brains of rabbits beyond the third passage. It was not considered necessary to carry this strain further and so no more inoculations were made, the strain being preserved in neutral glycerine in the refrigerator.

On May 29, Dr. Ambrosio Reyes invited us to see a case of human rabies under his care here in Manila.

The patient, a little boy 8 years old, while playing on April 5 with other children in a street near his home, was bitten on the left forearm by a strange dog that ran in among the children. The wounds were cauterized with carbolic acid and they healed in eight days. On May 27, vesicles were noted over the site of the bite. This herpetic eruption traveled up the forearm and arm, over the left pectoral and left scapular regions, and finally up onto, and behind, the left ear. The lesions itched intensely and the boy scratched them, leaving an abraded surface from which a thin, clear serum exuded. In the afternoon and evening of May 27, the boy became drowsy and did not care to play. The next morning there was difficulty in swallowing, and the parents, recognizing that the boy was developing rabies, called Doctor Reyes. On May 29 the boy was unable to swallow. Water taken into the mouth caused a spasm in his throat and he immediately spat the water out. There was almost complete suppression of urine. On May 30 the sight of water or food would provoke a severe spasm and the boy died in a convulsion on the evening of May 30.

The case clinically was one of typical rabies, and Doctor Reyes recognized it as such on May 28. He informed us that this is the eighth case of human rabies he had seen in a private practice of twenty years in Manila. From his early and accurate diagnosis in this case, there is every reason to believe that all of his other seven cases were rabies.

Negri bodies were not found in the brain of this boy, but an emulsion of the brain injected subdurally and intramuscularly into rabbits killed all of them with typical rabies in from fourteen to twenty days. Negri bodies and Lentz passage bodies were readily demonstrated in the brains of these rabbits. This strain was carried through three passages in rabbits between May 31 and July 18, all of the last passage rabbits dying of typical rabies in about two weeks. It was not considered necessary to carry this strain any further, so no more inoculations were made, it being preserved in neutral glycerine in the refrigerator.

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[5] Dudley and Whitmore: Rabies in the Philippines. A Preliminary Report, read before the Manila Medical Society, May 2, 1910. *Bull. Manila Med. Soc.* (1910), **2**, 99.

We had now shown so conclusively that rabies does occur in dogs in the Philippine Islands and in the human in Manila that it was necessary for us to secure a strain of fixed virus and carry it along in Manila. It did not seem advisable to wait for one of our own strains to become "fixed," as a year or more probably would be required to reach that end; and four attempts to bring in a fixed virus had already failed, the virus in each instance losing its virulence en route or else very soon after its arrival. Accordingly, one of us (Whitmore) was sent to Saigon, French Indo-China, to study the methods of the Pasteur Institute for preventive treatment of rabies and to bring back if possible a fixed virus in animals and in glycerine. The fixed virus in use at Saigon was brought out from the Paris Institute some months ago. It had gone through upward of eight hundred passages in Paris and fifteen in Saigon.

Rabbits were inoculated subdurally with fixed virus at the Saigon Institute and were placed on a boat sailing directly for Manila. At the same time fixed virus was placed in a bottle of neutral glycerine in a refrigerator on the same boat. The rabbits arrived in Manila in good condition and died of experimental rabies in the Biological Laboratory, Bureau of Science.

The fixed virus in glycerine had preserved its full virulence and when inoculated subdurally into rabbits in Manila killed them in about ten days. The brain tissue from the imported rabbits was also fully virulent when inoculated into rabbits here. This strain of fixed virus has now passed through five passages of rabbits in the Biological Laboratory, Bureau of Science, and constantly kills rabbits in about ten days, with typical symptoms of experimental rabies. This strain is being used for the protective inoculation against rabies which is now being carried on in Manila.

SUMMARY.

1. We have shown conclusively that rabies occurs among dogs in the Philippines, (*a*) by finding Negri bodies in the brain tissue of two dogs killed for suspected rabies; (*b*) by carrying the virus from the brains of one of these dogs through seven passages in rabbits, rabbits of the seventh passage dying in nine days of typical experimental rabies; (*c*) by demonstrating the presence of Negri bodies and Lentz passage bodies in the brain tissue of these rabbits up to the third passage.

2. We have shown conclusively that rabies does occur in the human in Manila, (*a*) by observing a case that was clinically typical rabies;

(*b*) by carrying the virus from the brain of that case through three passages in rabbits, the rabbits of the third passage dying of typical experimental rabies in about two weeks; (*c*) by demonstrating the presence of Negri bodies and Lentz passage bodies in the brain tissue of three rabbits up to the third passage.

3. We have succeeded in bringing a fixed virus from Saigon to Manila in animals and also in neutral glycerine in a refrigerator. The virus brought in both ways has retained its full virulence since its arrival here. By means of this work it has therefore been made possible to carry on protective inoculation against rabies in Manila.

NOTE.—Ashburn and Craig reported in the Military Surgeon, June, 1907, vol. 21, p. 529, as follows:

"*Rabies.*—On the 7th of June we obtained from the land transportation corral, quartermaster's department, Manila, the body of a dog thought to be dead of rabies. The animal had been under observation during the entire period of its illness and the symptoms and history both indicated that it was suffering from the disease mentioned. Examinations of smears from its brain, according to the method spoken of as affording 'a rapid diagnosis of rabies' showed bodies corresponding in form, size, and staining reaction with the description of Negri bodies. Cerebral inoculation of three rabbits with the same brain substance, however, has failed to induce in any one of them any symptoms of rabies or of other disease."

In their quarterly report ending September 30, 1907, to the Surgeon-General, United States Army, they further state:

"In our last quarterly report we recorded some observations on the examination of the brain of a supposedly rabid dog. The brain showed bodies indistinguishable from 'Negri bodies' and, as intracerebral inoculation of four rabbits had not induced the disease in them after a period of twenty-three days, we concluded that the bodies were probably not Negri bodies, or, if so, that they were not necessarily indicative of rabies. Since that time, however, all four rabbits have died of the disease, and, by the passage through other animals, Doctor Ohno has somewhat increased the strength of the virus and lowered the period of incubation.

"Our observations in this one case, therefore, go to emphasize the diagnostic value of the Negri bodies, rather than to belittle it."

It will be noted that the dates on which the rabbits were taken ill and died are not given. Nothing is said about the microscopical examination of the brains of these rabbits. In any event the rabbits died some time after the twenty-third day and for this reason alone Ashburn and Craig were in all probability not dealing with true rabies. In the work here all of our rabbits developed the disease between the twelfth and seventeenth day (most of them on the fifteenth day). None died later than the twentieth day. If Ashburn and Craig had been dealing with rabies, some of their rabbits would certainly have shown illness before the twenty-third day.

Doctor Ohno in a report to the Director of the Bureau of Science, dated July 9, 1907, evidently referring to these same experiments (however, only accounting for three of the four rabbits), states that three rabbits were inoculated on June 8. One developed "slightly typical symptoms" on June 29, twenty-one days after inoculation. He does not state whether this rabbit died or was killed. The second rabbit developed "slight symptoms" on June 30 (twenty-two days after inoculation) and was killed by chloroform on July 1. The third rabbit is recorded in his table as having succumbed July 9, thirty-one days after inoculation. It is not stated whether it died or was killed by Doctor Ohno. It will be noted, Ashburn and Craig stated that these rabbits died after the twenty-third day. Nothing is said about the microscopical examination of the rabbits' brains for Negri bodies. This report serves to confirm the opinion expressed in the foregoing.*

F. W. DUDLEY.

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* The report made by Doctor Ohno was received in the absence of the Chief of the Biological Laboratory and is printed at the end of this number. (Ed.)

ILLUSTRATION.

EXPLANATION OF PLATE I.

Section through hippocampus of rabbit which died twenty days after intramuscular inoculation of emulsion of brain of dog number 1. Stained with eosin-methylene blue, according to Lentz's method B. Zeiss: Compens.-ocular 12, obj. apochromat. 2 mm homog. Immers. N. A. 1.30, Tube length 160 mm.

The nerve cell to the right at the top shows marked degeneration. The nucleus stains a dull violet and is not marked off from the cell protoplasm, while the nucleolus stains deeper blue than in the other nerve cells. The "body" in the upper part of the cell stains faintly and has four rather large "inner bodies," while one "inner body" in the lower "body" is unusually large. These bodies are probably closely related to the Lentz passage bodies.

The Negri body in the cell on the left of the plate lies on top of the nucleus.

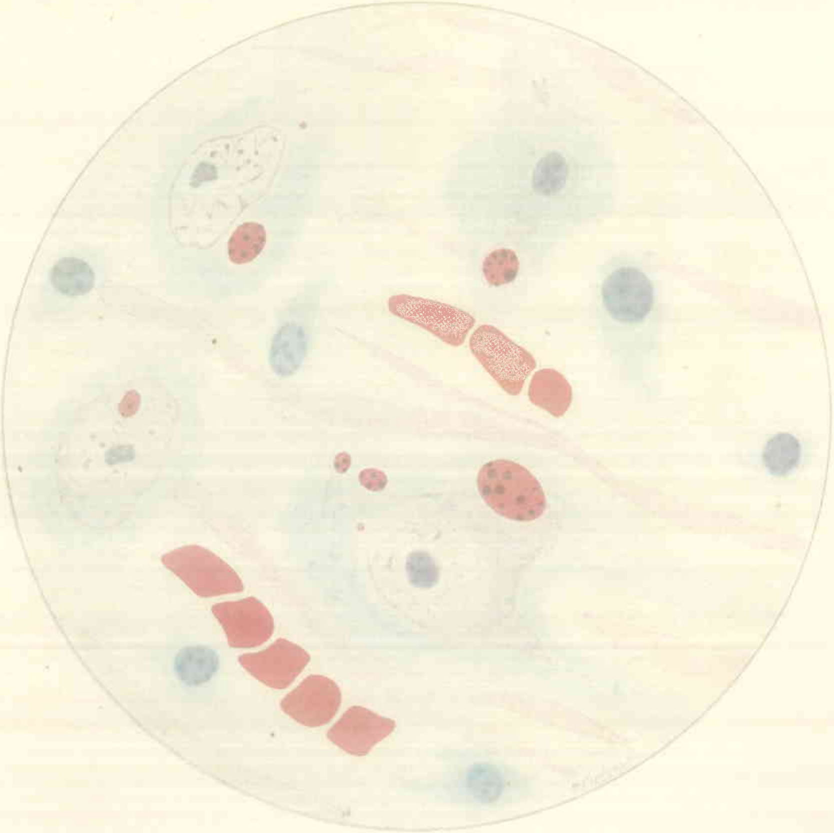

PLATE I.

RESEARCHES ON ACARIDS AMONG LEPERS.

By M. **Lefebvre.**

(From the Biological Laboratory, Bureau of Science, Manila, P. I.)

M. Borrel in 1909 published two very interesting papers, "Acariens et Cancers" and "Acariens et Lèpre,"[1] in which he proposed the hypothesis based on noteworthy observations, that the agent of propagation of both these diseases might be an acarian parasite, namely, *Demodex folliculorum* Simon.

I have taken up the critical examination of this hypothesis so far as it concerns leprosy. The materials for the present investigation have been taken from lepers of the San Lazaro Hospital in Manila. The following methods principally were employed in their collection and study.

1. *Contents of the sebaceous glands collected in vivo.*—To extract the contents of the sebaceous glands, I usually made use of glass tubes, one end of which I reduced to a filament having an interior diameter of 2 millimeters. By properly pressing this open end on the skin so that it circumscribed the opening of a sebaceous gland, the entire product of the gland was forced up into the tube, and the contents of the latter then pushed by a straw onto a microscopical slide. The individuals of Demodex, if there are any, are by this means almost certain to be extracted, for they are always found at the bottom of the sebaceous cavities.

There is a chance of at least one error in the microscopic examination of this substance, for it often happens that in the mass of sebum there occur small, molded portions which so closely resemble the body of Demodex that it is nearly impossible to distinguish them from it, and all the more so because the granulations and the greasy consistency of the mass make it indistinct. Hence it is necessary to clear the preparation by a solvent. After various trials with ether, alcohol-ether, chloroform, potassium hydroxide, potassium carbonate, borax, etc., I decided on a solution of borax; the greasy substance disappeared by its use and it was easy to recognize the bodies which remained after the treatment.

2. *Cutaneous nodules excised from living lepers.*—Nodules not yet ulcerated must be chosen. The ablation is often almost painless, as many of them are anæsthetic.

3. *Pieces taken at autopsy.*—The lobes of the ear; sides of the nose; pieces of skin cut off around the various nodules; portions of the characteristic moniliform nerves, and internal organs, the spleen in particular, were used in order to compare the bacilli found therein with those observed in the skin.

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[1] *Ann. Inst. Past.* (1909), **23**, 100, 127.

I employed Borrel's fixative, the formula of which is given below, for the small pieces of tissue taken either from the living or dead body:[2]

	Grams.
Water	350
Osmic acid	2
Chromic acid	3
Platinum chloride	2
Glacial acetic acid	20

However, I prefer Meyer's acetic acid sublimate solution which consists of a saturated solution of bichloride of mercury, 100 cubic centimeters, and acetic acid, 0.5 cubic centimeter. This solution fixes well and interferes less with the staining of the sections.

The sections were for the most part either stained by the Ziehl-Neelsen method, or with eosin and crystal violet and Gram's iodine solution. This second process is the best for the study of the bacilli.[3]

I.

The first important question to decide was what percentage of both leprous and healthy individuals in Manila harbored Demodex. A research of this character among healthy people has been attempted elsewhere by several investigators. I have not had the means of doing so under favorable conditions in Manila. I might have tried, it is true, in a hospital, but the results would not have been above criticism, for all parasitologists know the great influence of the morbid state on the number of organisms living even in organs untouched by disease; and in the case in question it is particularly necessary to keep in mind that lymphatic, scrofulous, arthritic and many other affections also modify the quantity of the sebaceous matter, in which *Demodex folliculorum* lives.[4]

The results regarding the prevalence of Demodex published by different authors vary exceedingly. Gruby[5] says he found *Demodex folliculorum* in the sebaceous glands of 40 among 60 persons he examined. Moniez, and also Raillet,[6] considers this a greatly exaggerated number. Mégnin,[7] according to researches made on a regiment of artillery composed of men from all parts of France, gives an average of 1 out of every 10 individuals having Demodex. Borrel examined 20 individuals of different ages between 20 and 70 years and estimated the average at 50 per cent; it is to be noted that the subjects of this last research were hospital patients. Borrel also examined a large number of cases of epithelioma and found the percentage infected to be increased. I shall refer below to his researches on lepers.

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[2] Acariens et Cancers. *Ann. Inst. Past.* (1909), 23, 100.

[3] Baumgarten's process, recommended for differentiating the bacillus of Hansen from that of Koch, sometimes gives misleading results. I have found, as several observers have already noticed, that tubercle-bacilli as well as the bacilli of leprosy are often stained by this process.

[4] Berlioz. Man. prat. des maladies de la peau. 3 ed. (1894), 160.

[5] *Compt. rend. Acad. Sc.* Paris (1845), 20, 569.

[6] *Zool. Med.* (1895), 635.

[7] Parasites et maladies parasitaires (1880), 272.

My personal investigations, although not conducted systematically enough to furnish a very definite conclusion, indicate that, exclusive of children, Demodex does not live on more than one-quarter of the individuals who are in health.

I believe that the apparently great differences existing between these various statistics, for instance, between Gruby's report of 66 Mégnin's of 10 per cent, are due to slight errors which have not sufficiently been taken into account. I pointed out one of these when indicating the preferable technique which will make such an investigation fairly successful.

However, an important fact, admitted by all observers, and one which does not agree with Borrel's theory, is that young children never are the hosts of Demodex. Now, many cases of children attacked by leprosy have been noticed; according to Sauton the disease often manifests itself in them at the early age of 4 or 5 years.[8]

It may be interesting here to report some observations on the kinds of sebaceous glands inhabited by Demodex. In this connection, we must distinguish between normal sebaceous glands and obstructed ones which give birth to comedones (blackheads) and to the different varieties of acne. The parasite often lives in perfectly normal glands.

Comedones (blackheads) are formed in glands the openings of which have been obstructed, and as the glands continue to secrete, they sometimes swell by the accumulation of their own products. The plug is formed by a portion of sebum which has hardened in the same way that the majority of vegetable and animal oils thicken by contact with the air, that is, by oxidation. The formation of this plug is assisted by dust which adheres to the surface of the sebum. This explains the more frequent existence of comedones on persons who are careless in personal cleanliness. However, want of cleanliness is not the principal cause of comedones; they are influenced chiefly by personal predisposition, either because the sebum of certain individuals is naturally thicker, because dust sticks to it more readily, or because it contains substances which tend to harden more rapidly by oxidation. For instance, one meets people of the upper classes who are exceedingly careful in their personal habits, but who suffer great annoyance, from comedones and on whom they persistently reappear in spite of every care. On the contrary, there are workmen and beggars who certainly do not wash every day who have no comedones. I may also add, that persons subject to fatty seborrhœa, not too intense, provided they wash the face with care, often have no comedones in spite of the abundance of sebum; this is probably because the latter is soft and rapidly evacuated.

I mention these well-known and apparently insignificant details to show that Demodex may wrongly have been designated as the cause of comedones. Besides, and this brings us back to our subject, in studying the content of some hundreds of sebaceous glands, I found Demodex much oftener in normal ones, with open orifices, than in comedones. Balzer had already noted the same thing. This might have been expected

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[8] Sauton. La Léprose (1901), 327.

a priori. The invasion of a sebaceous gland by the larva or eggs of Demodex being possible only by the orifice of the excretory duct, those glands which are obstructed by comedones are protected from infection. Any parasite found in them can only have penetrated there before the formation of the plug.

If parasites which have previously penetrated glands bearing comedones should generate larvæ, the larvæ can not spread until after the expulsion of the comedone. Now, the latter are known to persist sometimes for months; indeed, I have met with some that I could extract only with the bistoury. Old comedones are often definitely encysted and the gland ceases to perform its function. In short, comedones are not habitually due to Demodex and they are unfavorable to the propagation of this parasite.

However, I did encounter Demodex on a leper who had severe acne molluscum which had infected a great part of his face, but the sebaceous glands taking part in this acne performed their functions abundantly and on the slightest pressure their product escaped easily.

I have been able more precisely to fix the percentage of lepers having Demodex than I have that of persons in health harboring this organism. My observations have been made on a hundred lepers. I collected the product of the sebaceous glands from all parts of the body, but more especially from the sides of the nose and the ear. To judge from this series, the average percentage of lepers harboring Demodex does not seem to exceed 25.

I must say that in this search for Demodex on lepers Borrel has been more fortunate than I. He says, "Among the lepers we examined, we each time found Demodex in the follicles."[9] However, he does not mention the number of patients he examined. His investigation was made on the lepers in the Hospital Saint-Louis in Paris,[10] in so far at least as regards the direct search for Demodex in the follicles. The examination of microtomic sections of tumors was made from leprous nodules of the nose which he received from Algiers and Bergen. Borrel speaks only of one of these nodules, of which he gives an excellent description, but he does not say whether he found Demodex in the others, nor how many tumors he received. Therefore it would be difficult to form a statistical argument from his report "Sur les Acariens et la Lèpre." His discussion on the function of Acarina in Cancer is richer in material and, if one may reason by analogy between two such different diseases as leprosy and cancer, this comparison would afford some grounds for his hypothesis.

If the results of my researches on the lepers of San Lazaro are accepted, they will constitute a second unfavorable conclusion to Borrel's hypothesis, the first being that drawn from the absence of Demodex among young children.

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[9] Acariens et Lèpre. *Ann. Inst. Past.* (1909), **23**, 127.

[10] When I had the opportunity of examining the lepers at the Hospital Saint-Louis a few years ago, they were about fifteen in number. I do not know how many there are at the present time, nor whether M. Borrel looked for Demodex in all of them.

It seems, in fact, that if Demodex were either the principal or the only agent for the propagation of leprosy, this parasite would be found in all, or, at least, in the greater number of lepers. However, this objection thus formulated would be too absolute, as the reply might be made that the infecting parasite would necessarily exist in the skin of the leper at the time of infection, but might well disappear later during the evolution of the disease. *Demodex folliculorum* is not a migratory parasite, it never changes its home: the same follicle is its cradle and its grave. However, it might be that the leprous lesions, with their dreadful ulcerations, render the follicle uninhabitable, or possibly bring about the death of the parasite. This must be the case once the ulceration has appeared. I have never found Demodex in an ulcer however recently it has been opened.

For this reason I pursued my investigations principally on the sebaceous glands from parts of the body which either were healthy, or on those (especially the nose and ears) which were only beginning to show symptoms of leprosy, and also on the sound skin which covered the beginning leprous nodules. From this long series of examinations, which includes several hundreds of sebaceous glands, I obtained the following results.

As already stated, *Demodex folliculorum* was not of frequent occurrence, it being found only on about a quarter of the lepers. It was not more frequent in the follicles of the leprous parts on the face than in the corresponding healthy parts. It was never encountered anywhere in the body except in the glands of the face or ears, either upon direct examination of the contents of the sebaceous glands or of microtomic sections of young nodules excised either from the living or the dead; and, moreover, it was never found in the normal skin of the hands and feet, either of healthy persons or of lepers.

The leprous spots that are met with in anæsthetic leprosy in all infected parts of the body including the face, for example, the livid or colored spots, and those invisible areas recognizable only by their anæsthesia, are free from Demodex. There are even places where the sebaceous glands are half atrophied, shriveled, small, and performing their functions improperly.

On the other hand, I have sometimes encountered *Demodex folliculorum* in the glands of the nose, ears, and chin, when these parts were already manifestly leprous. In such cases they were often found together with the bacillus of Hansen. I also have seen *Demodex folliculorum*, together with the Hansen bacillus, in the enormous follicles of acne molluscum in the case mentioned above. This is noteworthy, because it shows that Demodex and the bacillus can live together, and consequently, that if the former is not always found in the nonulcerated leprous parts, it is not because the bacillus has made such parts uninhabitable for it, but simply because Demodex has not always been established there. Lastly, I have found this parasite also in healthy follicles on lepers, where microscopic examination did not show the bacillus of Hansen to be present.

In brief, *Demodex folliculorum* appears only in a quarter of the lepers. When present, it is encountered in those parts of the skin already attacked by leprosy, provided the leprous lesions have not as yet seriously disorganized the tissues. It can also be found in the parts and in the follicles free from leprous infection. It is often absent from those parts affected by leprosy, even when this infection is recent. It is to be noted particularly that *Demodex folliculorum* is never encountered in the skin of the hands and feet, the parts particularly prone to the lesions of leprosy.

It is evidently difficult to make the above observations harmonize with the hypothesis that *Demodex folliculorum* is the principal agent transferring infection in leprosy; but the study of the lesions of leprosy suggests another and more important doubt, which must at once have impressed the reader of Borrel's report. The latter was led, as he admits,[11] after his researches on the same subject in cancer, to suspect the infecting action of an acarid in leprosy. However, is there any analogy?

The cancers discussed in Borrel's paper are epitheliomatous; with the exception, perhaps, of cases of metastasis, they are primary lesions in the places where they are found. One can understand that an external parasite can have deposited, at the place itself, the yet unknown virus of cancer. Can the same be said of leprous lesions? Would a leprologist think that the phenomenon of the anæsthetic spots, for instance, has its origin in the skin? Certainly not: it is a nervous manifestation. The same must be said of the mutilations and deformations of the extremities which so terribly afflict the unfortunate lepers. They are trophoneurotic troubles in the mutilating lesions, paralyzing in the deforming ones. Even were it not physiologically evident, the many works which have appeared on the pathologic anatomy of the nervous system of lepers have amply demonstrated this fact. A striking and common symptom in the leprosy is the moniliform transformation of certain nerves of the limbs, for instance, the ulnar and sciatic; these are often found by palpation in the hyperesthetic period before the mutilations and the deformations have appeared.

If we now pass from these important lesions to the ulcers and from the latter to the nodules which preceded them, and then to the simple turgescences which preceded the nodules, the question arises: Is the cause of these phenomena to be sought for in the skin, or in the glandular apparatus? The microtomic sections of the nodules show them to be full of bacilli, their formation to be due to the accumulation of these bacilli, and, doubtless, also to their toxic products.

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[11] *Ibid.* 125.

Contrary to Una's theory, it is now known that the bacilli of leprosy, at least for the most part, are contained in the cells. Some authors even say that they are found only in the cells; this last opinion seems to me open to dispute, but it is unnecessary to discuss the question here; it is sufficient to state that the greater number of bacilli are intracellular and that in these cells they undergo a process of destruction; a very large number are separated into granules. Their aspect recalls *in vivo* Pfeiffer's phenomenon *in vitro:* agglutination and destruction. One can follow all the series of the stages of this disorganization, from the simple vacuolated form to the reduction into smaller dissociated granules. In short, there is an evident phagocytosis. This phenomenon appears more clearly in the sections treated with crystal-violet-Gram.

The first thought suggested by this examination is that the nodules are produced by a defensive reaction of the organism, just as are the pulmonary tubercles of phthisical patients; they are a means of first collecting, then destroying, and finally of eliminating the bacilli. Such is the opinion of many leprologists; and even if we admit, with others, that the cells of the nodules contain bacilli in process of multiplication, this must be looked upon merely as a case of accidental insufficiency in the action of the former. But if this be so, the skin of the leper should much more be considered as a means of elimination than as an open door for infection. It is true that Babès thinks that both these functions may be attributed to it, as we shall show below.

Although it is a slight digression, I wish here to compare the sections from cutaneous nodules with those taken from the tissue of the spleen. It seems that the spleen also has a defensive function in leprous infection, as in several other diseases. It is certainly a collector of bacilli: the circulation brings them to this organ as to a storehouse. A very large number of these organisms are still perfectly normal, scarcely vacuolated;[12] next to them one finds others, more or less dotted, and a great quantity of others in fragments up to the final stage of reduction.

Other organs of the body also work with the same defensive aim; one sees such a process in the nodules of the moniliform nerves. At one autopsy I likewise collected numerous calcified concretions on the peritoneum, which contained the bacillus of Hansen undergoing destruction.

It appears that the spleen can exercise a defensive function better than the skin or nerves, perhaps because of a more energetic activity which it possesses in the work of destroying the bacilli, and in consequence also of the abundant circulation of which it is the seat. The spleen also seems better protected from the serious hypertrophies which manifest themselves in the cutaneous tissues and in the nerves. The nodules of the moniliform nerves are due to the accumulation of the bacilli and to their toxic products, but in this situation the bacilli can remain, as there is no powerful circulatory current compelling them to move. The same conditions surround the cutaneous nodules and the latter, after having defended the organism by localizing and digesting the bacilli, end by becoming victims of their own work; the cells deteriorate and succumb for want of power to rid themselves rapidly enough of the parasites and their products. Such deteriorated cells can be seen in all sections of the cutaneous nodules. The nodule in the end becomes disorganized and degenerates into an ulcer.

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[12] All normal bacilli seem more or less vacuolated when the staining of the sctions has not been sufficiently prolonged, or when the decoloration according to the method of Ziehl or Gram has been carried too far. On the contrary, with good staining, one always finds many individuals uniformly colored.

The conclusions to be drawn from these theoretical views and the observed facts may be summed up as follows:

1. The external lesions of leprosy, not only the deformations, the mutilations and the anæsthetic areas, but even those disturbances which end in the formation of the cutaneous nodules, do not primarily originate at the point where they are observed, but are dependent on deeper causes, some simply nervous, others circulatory.

2. The accumulation of leprosy bacilli in the hypertrophies of the skin is the result of *an exportation from the interior of the organism,* the object of these formations being to localize, to destroy, and to eliminate the bacilli.

It seems as if this reasoning is but an argument against the theory of the transmission of leprosy by means of the skin. I do not wish to overrate its value, for I myself retain doubt on the question.

Although these ideas are fairly generally accepted by authorities on leprology, it must be acknowledged that they contain as much theory as observation. Now, a theory is most useful in guiding the seeker, but nothing is more dangerous than to regard it as an accepted truth, instead of a means of arriving at the truth. Moreover, I do not wish to present my observations as conclusive, for, if I believe others to be mistaken, I see no reason why they should not think the same of me.

If the cutaneous lesions of leprosy are reactions due to internal, nervous and circulatory causes, it does not follow that the contagion may not first of all have entered through the orifices of the skin, for it may be true that the first bacilli enter by means of the skin in the neighborhood of the parts where the nodules afterwards have formed. One can imagine these organisms gaining admission through the sebaceous glands, then penetrating deeper into the tissues and multiplying there, and lastly, a part of them stopped in their migration, and brought by the circulation into the parts near which they had entered. This would more or less explain the only fact which seems to favor the theory of infection through the sebaceous glands: namely, the parts where the first manifestations of leprosy are found are the sides of the nose and ears. However, it must be acknowledged that this hypothesis is purely without foundation. I suggest it, because in doubtful questions no possible hypothesis should be neglected. Cornil and Babès in 1888 thought that the integument, the sebaceous glands, and the follicles of the hairs in particular are a means, not only of elimination, but probably of the penetration of the bacilli also.

Whether this theory is true or not, I think I may conclude from all that precedes, that (1) it is difficult to reconcile the observed facts with the hypothesis that *Demodex folliculorum* is the principal agent of leprous contagion; and (2), that no positive argument can be drawn from the existence of external leprous lesions to prove that contagion takes place by way of the skin.

II.

So far we have considered Borrel's theory of the contagion of leprosy by acarids more particularly with regard to the place where the bacilli might be introduced and where they might multiply. It remains for us to consider the agent itself, which Borrel supposes to be the bearer of the contagion, and to ask if it possesses the qualifications necessary for this function.

The genus Demodex, the only one of the family *Demodecidæ,* comprises only one species, *Demodex folliculorum* Simon, which is divided into several vareties, of which only one appears to live in the human skin, the var. *hominis* Simon.

Besides Demodex, the acarian parasites of the human skin thus far encountered are the following: *Sarcoptes scabiei* Latr., parasite of the itch, Sarcoptes of the Norwegian itch, the identification of which is uncertain and which perhaps is only a variety of *Trombidium holosericum* Herm.; various species of Ixodes and Argas. There are probably some other acarian parasites of man as yet but little understood. Demodex is the only fixed acarian parasite known to live in the human skin; the others cited are all more or less migratory.

Borrel states as follows: "Lepers must be infected by Demodex or other fixed acarids. I found it impossible to determine on the sections, the species or variety of the parasites I saw."[13] Why should the suspected parasite be fixed? Is not a migratory acarid more to be feared? It is precisely this sedentary character of *Demodex folliculorum* which seems to me to afford the best argument against Borrel's theory. We have seen that one often meets with areas of the skin quite recently attacked by leprosy, the follicles of which contain no Demodex; this fact would easily be explained if the acarid, bearer of the contagion, were migratory; it can not be explained if it is fixed. Besides, how should Demodex carry the contagion from one person to another?

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[13] *Ann. Inst. Past.* (1909), **23**, 127.

Borrel states that the conditions of migration of Demodex are unknown.[14] It is true we have not as yet a complete account of its life history, but the few facts which seem well established are sufficient to show that *Demodex folliculorum* stays at home. No observer has met with it outside the sebaceous glands. For my part, I have often examined the scrapings of the skin near the glands containing Demodex; and I did so periodically in the particular case of an individual infected with the parasite, but with negative results.

Moreover, the anatomy of Demodex renders it unfit for the work; its legs, consisting of only three very short articulations instead of five as with the migratory acarids, such as *Sarcoptes scabiei,* are exceedingly small; they resemble little conical tubercles and it seems hardly possible that they could carry the animal's enormous abdomen. In fact, when Demodex is observed under the microscope, it is very easy to see the difficulty it experiences in moving even a few tenths of a millimeter, and this difficulty is increased by the mass of sebum in which it is embedded. Therefore, the individuals of Demodex are prisoners, so to say, in the sebaceous gland in which they have been developed, living normally in the lowest parts, with the head generally turned to the bottom. Their reproduction takes place in their prison. Nathan Banks thinks that, if the Demodex lays eggs, they must be fusiform,[15] but I think he is mistaken. I have never met with true eggs of the parasite; one must probably admit with Mégnin[16] that what have been taken for eggs really are apode larvæ. As these develop, they acquire six little unarticulated papillæ which represent the legs, and then, by successive moults, the eight pairs of articulated legs of the adult.

These larvæ are carried out of the gland with the mass of sebum as it escapes, little by little, and they alone could transport the contagion of leprosy, but only in the same way as the sebum itself, and the residue of the cells and other particles that it contains could do the same thing. Evidently the sebum, the particles, and the Demodex larvæ may be covered with the Hansen bacilli and may disseminate them; but this would result only in a passive contagion. The idea then must be abandoned that Demodex is an active propagator of leprosy, as, for example, is, in some diseases, the mosquito or glossina which has sucked the virus of a patient and which then inoculates another individual by stinging him.

I have often looked for the Hansen bacillus in the body of Demodex, but without success; I can not say that it never penetrates the body, for to prove this would be difficult, but the preceding considerations render this question unimportant.

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[14] *Ibid.*

[15] A Treatise on the Acarina or Mites, *Proc. U. S. Nat. Mus.* (1905), **28**, 1.

[16] *Loc. cit.*

I have had no opportunity to study the migratory acarids cited above from the point of view of leprous contagion, except *Sarcoptes scabiei.*

This acarid is essentially migratory. The female alone forces its way into subepidermic tunnels which she has burrowed for the purpose of laying her eggs, and remains in this situation until she dies; the male raises a small epidermic pellicle under which he hides, but this is only a temporary shelter and he soon leaves it to form a similar one elsewhere, and so on. The remainder of the life of these parasites is passed on the surface of the skin.[17] Here, no *a priori* objection can be raised against leprous contagion by the medium of the Sarcoptes of the itch. It is a mere question of fact.

I observed an epidemic of the itch among the lepers of San Lazaro and learned from questioning them that the greater number of the lepers then afflicted with the disease did not have it before entering the hospital as leprous patients; moreover, I saw the itch in an early stage on several of the lepers. Finally, several of the lepers told me that they had never had the itch previously. If their assertions can be trusted, I must at least conclude that the Sarcoptes of the itch is not the normal agent of leprous contagion.

I have sometimes encountered the Hansen bacillus in the parts affected by the itch, particularly when a leper, by scratching, has caused erosions which suppurated; but as the erosions were in the immediate vicinity of leprous ulcers, it is not proved that the bacilli had been imported by the Sarcoptes. I have never found the Hansen bacillus in the itch furrows formed in parts not previously leprous. On triturating bodies of Sarcoptes for bacteriologic examination, I did not find the bacillus of leprosy.

Finally, I treated and cured several cases of itch on lepers, and after the disappearance of all signs of the infection, the healed parts after an observation carried on for several months showed no symptoms of leprosy. However, evidently no great importance can be attached to this last statement, as we are entirely ignorant of the duration of the incubation period of leprosy.

From all this, only a negative conclusion can be reached, since we have no conclusive proof that the Sarcoptes of the itch is the normal agent of leprous contagion; but neither is there proof that it can not transmit leprosy accidentally.

There remain two other acarids which I have encountered among lepers, but which, for want of sufficiently detailed literature, I can not determine definitely. One is of a species of the genus Tyroglyphus, the other of a species similar to this genus.

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[17] Mégnin, *loc. cit.* 219.

I sometimes met with the first species in leprous ulcers. I found it also in many cases of suppurative dermatitis following an infection of the itch and in the erosions caused by scratching. Some of the cases were very severe, and one might even have thought the lesions to be leprous manifestations; the feet and the lower part of the legs in particular were tumefied, very painful, the derma was exposed in many places and yielded a continuous flow of seropurulent fluid. The fact that two or three of these patients had leprous ulcers coexisting on the feet made it all the easier to mistake this infection for an exacerbation of acute leprosy. However, this disorder was due solely to the acarid of which I speak; in fact, the bacteriologic examination of the pus, of the serum, or of the scrapings of the diseased parts revealed no Hansen bacilli except at the precise place of the preëxisting leprous ulcers; the disease yielded in a few days to the specific treatment for itch, and nothing was afterwards seen on the skin except the well-defined leprous ulcers which were there previously.

This is not the first time that the presence of Tyroglyphus or some other saprophytic acarid has been remarked in ulcers, or in neglected sores, as is evidenced by all doctors who have treated sores of long-standing, ulcers, cancers, etc., among the poor and persons not scrupulously clean. Leprologists themselves have often noticed it. I call attention to it because of one point which touches on our subject; that is, that neither in analyzing the pus nor in examining acarians themselves, was I able to discover the Hansen bacillus except at the exact place of preëxisting leprous ulcers, or in their immediate vicinity. This fact is all the more significant because Tyroglyphi are very migratory acarians and even fairly active ones, and also because the suppurative dermatitis is confluent with leprous ulcers.

From this statement it seems that Tyroglyphi also should be eliminated from the number of normal bearers of the contagion of leprosy.

I wish merely to mention the other acarid of which I spoke and which appears to be similar to the genus Tyroglyphus. It presented an unexpected characteristic, for I discovered it not in open ulcers but in the serum from small, closed phlyctenæ. I was unable, in any of my observations with the magnifying glass, to find the opening by which this parasite made its way through the epidermis. As it was found on two patients infected with the itch, and as these phlyctenæ were near the furrows of the itch on one patient especially, it is a question whether there is any connection between its work and that of the Sarcoptes or just what this connection may be. Certainly there is no relationship, for these two parasites differ as much from each other as does Sarcoptes of the itch from Tyroglyphus. On the other hand, this new acarid, judging from its habitat, is not a saprophyte, but a parasite. No acarian parasite within the human skin is known at the present time except Sarcoptes of the itch and Demodex.

ON THE OCCURRENCE OF AN ACCESSORY NASO-FRONTAL DUCT OF THE FRONTAL SINUS.[1]

By ELBERT CLARK.[2]

The great variability in the size and extent of the frontal sinus, its position within the frontal bone and its relation to the ethmoidal cells have been well shown by Killian,(2) Onodi,(6) and Zuckerkandl.(12) This structure is indeed so variable that one is inclined to ask if there is any one type of frontal sinus which may be considered normal or distinctly typical. Therefore, it is not surprising that a difference in nomenclature as well as often some confusion have arisen. It has recently been shown by Wilson(10) that the nasofrontal duct and the ostium frontale are subject also to almost as great variations as the frontal sinus; and further, that in approximately only 55 per cent of the cases that cavity in the frontal bone, usually termed the frontal sinus, is drained by the duct which is the upward continuation of the infundibulum ethmoidale. In the other 45 per cent it opens into the middle meatus.

In the anterior ethmoidal region in the immediate vicinity of the sinus frontalis the number of ethmoidal cells (including the sinus frontalis) may vary from one to four (rarely five); these are variously known as bullæ frontales, anterior ethmoidal cells, etc. They are termed frontal cells by Killian.(2) They usually open into a common vestibule, more or less well developed, and are often fused and communicating in their upper portions. In the fœtus and infant they are seen as membranous evaginations from a slight ethmoidal bulla at the upper extremity of the infundibulum ethmoidale. These Killian(5) designates as the first, second, third, and fourth frontal cells. Either one of these cells may be represented in the adult by the frontal sinus. The frontal sinus may develop from the *Anlage* of either, the relations in the adult varying accordingly. This cell is usually the largest of the four and in a majority of these cases is a direct continuation of the infundibulum. That frontal cell which is located within the frontal bone is termed by Killian(2) the sinus frontalis, although it may not open into the infundibulum ethmoidale. The frontal sinus in this instance is not to be considered as one of the frontal cells. In many skulls four of these anterior ethmoidal cells are seen.

The present dissection was made on a specimen from a negro subject which was preserved in Kaiserling's fluid, allowed to dry for two weeks and softened by standing overnight in water. The drying seems to make the specimen more suitable for the separation of the membranous from the bony structures. It is possible by this method to chip away as much of the bone as is desired, leaving the membranes of the nasal and accessory nasal cavities undisturbed in one continuous piece, the relations of which are then easily determined. A successful preparation is obtained more easily in this manner than after mere preservation in formalin without the drying. In a subject that had been preserved in 50 per cent formalin and dried for two years, the membranes lining the frontal, maxillary and sphenoidal sinuses, the ethmoidal cells and nasal passages were entirely freed from bone, and a membranous model of all these cavities was obtained in one unbroken piece which was mounted on a portion of the occipital bone left undissected. In the negro subject the supraorbital ridges were prominent and the skull, nasal and cheek bones thick. The frontal sinuses of both sides were fairly large, of about equal size and approached the median line where they were separated by a thin lamina of bone.

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[1] Published from the Anatomical Laboratory, Philippine Medical School, Manila, P. I.

[2] From the Hull Laboratory of Anatomy, University of Chicago.

The frontal sinus of the left side (see Pl. I, fig. 1) is 30 millimeters in its mesial-lateral diameter, 28 millimeters in the saggital, and 12 millimeters in the antero-posterior diameter. Its lower surface is on a level with the cribiform plate and is 8 millimeters above the fronto-ethmoidal suture. On either side a middle and a posterior ethmoidal cell,[3] which opens into the superior meatus, covers over the entire roof of the orbit behind the frontal sinus. The other ethmoidal cells are small, as are both maxillary sinuses. The sphenoidal sinuses are not excessive in size. The left frontal sinus opens through the nasofrontal duct into the infundibulum ethmoidale. Its relations are those usually given for this sinus. The frontal sinus on the right side is in relation to three other frontal cells, the sinus itself representing the second cell. The first frontal cell is situated mesial and below and in close relation to the accessory duct of the sinus. (See Pl. I, fig. 1.) The third and fourth are small, narrow cells, 1 and 2 millimeters in diameter, respectively, and lie in close opposition to the posterior surface of the sinus frontalis, between it and the ethmoidal cells which cover over a greater part of the orbit. (See Pl. I, fig. 2.) The first, third and fourth frontal cells open into a small vestibule which is a direct continuation of the infundibulum ethmoidale. The frontal sinus (second frontal cell) on its posterior inferior funnel-like surface also communicates with the vestibule through a very short rudimentary nasofrontal duct. It presents a striking peculiarity in the occurrence and course of an accessory ductus nasofrontalis. Connection with the infundibulum and the middle meatus is attained only through the common vestibule of frontal cells 1, 2, 3, and

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[3] Ethmoidal cells of highest meatus of Killian's cellulae ethmoidates A and B, Plate I, fig. 2.

4, by the rudimentary nasofrontal duct just mentioned. The accessory naso-frontal duct arises from about the middle of the inferior surface of the sinus, 12 millimeters lateral from the median line. It takes a perpendicular course downward for 12 millimeters where, in a bulbous enlargement of 5 millimeters, it comes in close opposition with the saccus lacrimalis and the upper extremity of the ductus nasolacrimalis, and after curving through an angle of 90° extends medianward for 8 millimeters on the sutura frontolacrimalis just posterior to and above the ligamentum palpebrale mediale. Here it leaves the sutura nasofrontalis and runs downward, medianward and anteriorly in the os frontale and then beneath the os nasale to open into the anterior portion of the fossa nasale, 12 millimeters below the sutura nasofrontalis. The duct in its first course downward and medianward, after leaving the frontal sinus, curves around the first frontal cell above referred to and lies in close opposition to it, a very thin lamina of bone separating them.

The arrangement of the four frontal cells, of which the frontal sinus represents the second, will conform to the method of development of the frontal sinus from the infundibulum advocated by Killian, which is as follows: In the human fœtus five small ridges and six small furrows are to be seen on the lateral wall of the nasal cavity. In front of these is the small nasoturbinal elevation, and below all of these structures a long, narrow, horizontal ridge, the maxillo-turbinal. The maxilloturbinal gives rise to the inferior concha, the nasoturbinal to the aggar nasi and the processus uncinatus and the five small ridges to the middle and superior conchæ and to a fourth concha when present. The bulla ethmoidale develops posterior to the processus uncinatus and the adjoining first furrow and below the first ridge (the *Anlage* of the middle concha). The anterior furrow, on becoming deeper, thus forms the hiatus semilunaris and the infundibulum ethmoidale. By outward budding of the membrane there arise upon the anterior and superior aspects of the infundibulum the four primitive frontal cells. These are separated by narrow, incomplete septa, the infundibulum thus becoming a cavity with four branching evaginations. Further development is slow until about the age of puberty. The evagination which extends into the os frontale is termed the sinus frontalis. It may be either one of the four. The relations of the frontal cells in the adult vary accordingly. Killian terms this the indirect mode of development. When the infundibulum does not acquire the four evaginating appendages, but forms only one direct evagination anteriorly into the os frontale, there follows the direct mode of frontal sinus formation. In this latter case no frontal cells are present other than the sinus frontalis.

According to Mouret, that membranous evagination which develops first in the anterior ethmoidal region from the superior lateral wall of the nasal cavity forms the frontal sinus. The relation to the other ethmoidal cells and the variability of the nasofrontal duct are thus dependent upon

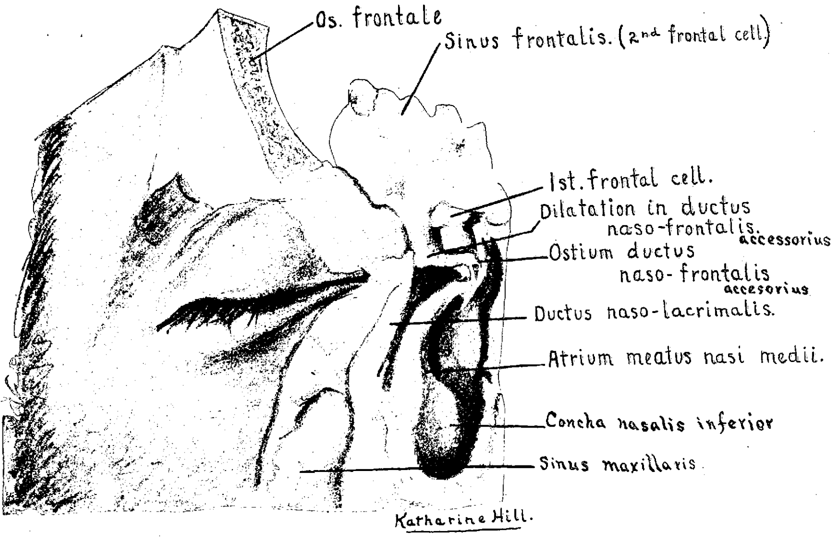
Os. frontale
Sinus frontalis. (2nd frontal cell)
Ist. frontal cell.
Dilatation in ductus naso-frontalis accessorius
Ostium ductus naso-frontalis accesorius
Ductus naso-lacrimalis.
Atrium meatus nasi medii.
Concha nasalis inferior
Sinus maxillaris
Katharine Hill.

FIG. 1.

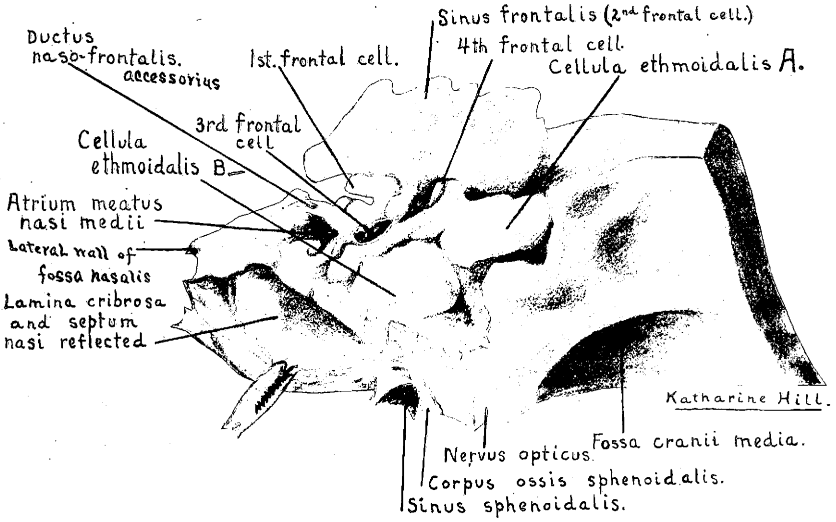

FIG. 2.

PLATE I.

A NOTE ON THE SPONTANEOUS OCCURRENCE OF BACILLARY DYSENTERY IN MONKEYS.

By Fred B. Bowman.

(*From the Biological Laboratory, Bureau of Science, Manila, P. I.*)

The epidemiologic factors in the etiology of bacillary dysentery are somewhat obscure. The sudden appearance of acute cases in districts usually free of the disease has been attributed to various causes. Drinking water and human carriers are known to be sources of infection and animals have been suggested as possible factors. The following report indicates that the latter may in reality be a source of infection for human beings.

During March and April, 1910, several cases of severe dysentery developed in monkeys kept in the animal house of the Bureau of Science. Two animals which had been used several months previously in an experimental investigation on trypanosomiasis were found in a condition of extreme prostration similar to that seen in acute human bacillary dysentery and were turned over to me for further study.

The animals were chloroformed and autopsies were performed. The following excerpts are taken from the protocols.

> Only the rectum and colon are affected, the small bowel shows no abnormal condition. The mucosa of the intestine is markedly injected, showing patches of hæmorrhage, and is covered with a sticky coating of bloody mucus. Microscopic examination of the fæces shows a large amount of mucus, some blood, leucocytes, and degenerated epithelium. Ova of *Œsophogostomum* are present and cysts caused by this parasite are seen in the intestinal wall.

Some of the mucus portion of the stool was suspended in salt solution and after a short time plates were made from the surface of this suspension, lactose-litmus-agar being used. In twenty-four hours no red colonies were present, the predominating type being extremely small, clear and blue. Cultures from the heart's blood, liver and spleen were negative. Control plates from the stool of a monkey apparently well showed large numbers of red colonies.

Cultures were made on agar slants from these small, blue colonies and later the following agglutination tests were performed, parallel ones being made at the same time with a typical nonacid-producing dysentery organism of the Shiga and an acid-producing one of the Flexner type. Antidysenteric sera from rabbits which had been immunized by Dr. E. R. Whitmore of this laboratory were used, one agglutinating specifically the acid type of organism and the other that of the nonacid type. Table I shows the dilutions employed and that the organisms from monkeys numbered I and II were both agglutinated by the nonacid strain, and in the same dilutions as the true acid strain used in the same experiment. They were not agglutinated by the Shiga serum.

Each organism was also tested as to its acid-producing and sugar-fermenting properties. (See Table II.) No acid was produced in lactose-litmus-agar, while the other four sugars used showed marked acid production. No gas was formed in any of the media.

No evidence is at hand which would indicate that these monkeys became infected from our laboratory cultures of the dysentery bacillus. A few rabbits were in the same animal house in the other end of the building. These animals had been inoculated subcutaneously with dysentery organisms five months previously, but they had never been placed near the cages containing these monkeys. The monkeys had been in the laboratory for months and it seemed highly probable that they had acquired the infection here.

If monkeys can be infected with bacillary dysentery, naturally it is not improbable that other animals may become carriers and give rise to the sudden appearance of this disease in previously noninfected districts. Only one observer has reported the production of the disease in monkeys by feeding experiments, and a search through the literature at hand fails to show a previous report of natural or spontaneous infection of monkeys with bacillary dysentery.

TABLE I.

Dilution	1-50.			100.			300.			500.			700.			900.			1,100.			2,200.		
Time (hours)	2.	5.	24.	2.	5.	24.	2.	5.	24.	2.	5.	24.	2.	5.	24.	2.	5.	24.	2.	5.	24.	2.	5.	24.
No. I organism:																								
Flexner serum	+ +	+ +	+ + +	+ +	+ +	+ + +	+	+ +	+ + +	—	+ +	+ + +	—	+ +	+ + +	—	+	+	—	—	+	—	—	—
Shiga serum	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Normal rabbit serum	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
No. II organism:																								
Flexner serum	+ +	+ +	+ + +	+ +	+ +	+ + +	+	+ +	+ + +	—	+ +	+ + +	—	+	+ +	—	—	+	—	—	—	—	—	—
Shiga serum	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Normal rabbit serum	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Shiga:																								
Flexner serum	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Shiga serum	+ +	+ +	+ + +	+ +	+ +	+ + +	+	+ +	+ + +	—	+	+ +	—	—	+	—	—	—	—	—	—	—	—	—
Normal rabbit serum	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Flexner:																								
Flexner serum	+ +	+ +	+ + +	+	+ +	+ + +	+	+ +	+ + +	—	—	+ +	—	—	+	—	—	—	—	—	—	—	—	—
Shiga serum	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Normal rabbit serum	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—

TABLE II.

Media	Glucose litmus agar.		Lactose litmus agar.		Maltose litmus agar.		Saccharose litmus agar.		Mannite litmus agar.	
Strains.	Gas.	Acid.	Gas.	Acid.	Gas.	Acid.	Gas.	Acid.	Gas.	Acid.
Shiga type	−	+ + +	−	−	−	+	−	+	−	−
Flexner type	−	+ + +	−	−	−	+ +	−	+	−	+ +
Monkey No. I	−	+ + +	−	−	−	+ +	−	+	−	+ +
Monkey No. II	−	+ + +	−	−	−	+	−	+	−	+

COMPLEMENT FIXATION IN YAWS.

By Fred B. Bowman.

(From the Biological Laboratory, Bureau of Science, Manila, P. I.)

There is still some doubt concerning the nosologic position of yaws; some eminent authorities believing it to be a modified form of syphilis, while others consider it a separate and distinct disease.

Castellani[1] in 1905 attempted to transmit the disease to a purple-faced monkey, but without success. However, in 1906, he was able to infect one out of three monkeys inoculated. This animal later was successfully inoculated with syphilis. Neiser, Bauerman and Halberstädter,[2] in 1906, found that all classes of monkeys could be inoculated with yaws and that monkeys immunized against syphilis did not become immune to yaws.

Castellani also applied the Bordet-Gengoŭ reaction to yaws, following the technique used by Wassermann, Neiser and Brück,[3] and was able to demonstrate specific yaws antibodies and antigen. The following is a brief summary of his results:

"I. Extract of nonulcerated yaws papules containing *Spirochæta pertenuis* + serum from a monkey infected with yaws + complement (fresh guinea pig's serum) and later, sensitized goat corpuscles. *Result:* No hæmolysis.

"II. Same as I, but in the place of yaws papules extract, extract of leprosy nodules used. *Result:* Hæmolysis.

"III, IV and V. The same experiment was performed, using extracts or pseudo-granuloma pyogenicum, syphilitic condylomata and syphilitic primary sore. *Result:* Hæmolysis.

"VI. Extract of yaws papules from six different cases of yaws and serum from a monkey immunized against syphilis. *Result:* Hæmolysis.

"VII. Extract of yaws papules and normal monkey serum. *Result:* Hæmolysis.

"VIII. Extract of Spleen juice from a case of yaws and serum of a monkey infected with yaws. *Result:* No hæmolysis.

"IX. Same as VIII, except that serum from a syphilitic monkey was used. *Result:* Hæmolysis."

Castellani sums up the preceding experiments by saying: "The above experiments show that it is possible to detect specific yaws antigen in the yaws papules and in the spleen of cases of yaws and specific yaws antibodies in the blood of monkeys treated with inoculation of yaws material."

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[1] *Journ. Hyg. Cambridge* (1907), **7**, 558.

[2] *Münchener med. Wchnschr.* (1906), **53**, 1337.

[3] *Deutsche med. Wchnschr.* (1906), **22**, 745.

"Experiments IV, V, VI, and IX show also that yaws antibodies and antigen are different from syphilis antibodies and antigen and therefore syphilis and yaws differ specifically."

In 1906[4] Landsteiner, Neisser and Poetzl used an alcoholic extract of guinea pig's heart in complement-binding experiments with serum from cases of surra. This extract when employed with serum from patients with syphilis gives a positive reaction in 80 per cent of the cases, but it had never been used with serum from those infected with yaws. Therefore, I decided to subject the sera of yaws patients to the complement fixation test with this extract, in the hope of throwing further light upon the relationship of yaws to syphilis. The sera were taken from four children and one adult with well-marked cases of yaws having the typical incrusted ulcer, in smears from which numerous *Spirochætæ pertenues* were found.

One gram of guinea pig's heart was ground finely and 50 cubic centimeters of 95 per cent alcohol added. The whole was then heated for three hours at 60 °C. and the clear fluid decanted. Red blood cells of the ox were used, and immune rabbit serum, which was hæmolytic when diluted 1 to 5,000, furnished the amboceptor.

Three preliminary experiments were always performed before the final Wassermann reaction, to determine the following:

1. Whether the extract was hæmolytic.

The extract was added to washed ox-blood cells in three dilutions, 0.4, 0.2 and 0.1, and allowed to stand one hour at room temperature.

2. Whether the extract inhibited hæmolysis.

The extract in dilutions 0.8, 0.4, 0.2, 0.1 and 0.05 + complement or fresh guinea pig's serum was allowed to stand one hour at room temperature (about 30° C.), then 1 cubic centimeter of a 5 per cent washed ox blood and 0.001 cubic centimeter amboceptor were added and incubated.

3. The serum to be examined 0.1 in each tube and salt solution 0.4, 0.2, 0.1 added in place of the extract and the whole allowed to stand one hour at room temperature. Then 1 cubic centimeter of washed ox blood and 0.001 cubic centimeter of amboceptor added.

It was found that the extract from the guinea pig's heart with the serum from cases of syphilis inhibited hæmolysis; that is, 0.1 cubic centimeter of inactivated serum from a case of syphilis + extract of guinea pig's heart (0.4, 0.2, and 0.1) + complement from fresh guinea pig's blood serum, and, in one hour, 0.001 amboceptor + 1 cubic centimeter ox-blood cells added, gave no hæmolysis. A parallel experiment performed at the same time, in which the same reagents were used, with the exception that yaws serum was substituted for the syphilitic serum, resulted in almost complete hæmolysis.

This experiment was performed many times, but always with the same result. These results demonstrated that serum from cases of yaws does not bind complement when the extract from guinea pig's heart is used.

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[4] *Wien. klin. Wchnschr.* (1907), **20**, 1420.

An extract of yaws papules was then prepared. One gram of papule was added to 5 cubic centimeters of salt solution containing 0.5 per cent carbolic acid and placed in a shaking apparatus for twenty-four hours. This was then centrifugated and the opalescent fluid decanted and placed on ice until ready to be used.

This extract was tested in the same way as the guinea pig's heart and was found to be nonhæmolytic and also noninhibitive.

The extract in three dilutions, 0.4, 0.2 and 0.1, was added to the sera from the cases of yaws (0.05 cubic centimeter) — 0.05 cubic centimeter of complement, and allowed to remain one hour at room temperature; then 1 cubic centimeter of washed ox-blood cells + 0.001 cubic centimeter amboceptor were added and all incubated at 37° C. for two hours and then placed on ice for twenty-four hours before the final reading was made. At the end of twenty-four hours it was found that there was marked inhibition of hæmolysis.

The following table summarizes the results obtained with the two kinds of extract:

Extracts used	Yaws extract.			Guinea pig's heart extract.		
Dilution of extract	0.4	0.2	0.1	0.4	0.2	0.1
Yaws sera	—	—	+ +	—	+ +	+ + +
Syphilis sera	+ +	+ +	+ + +	—	—	+ + +
Normal sera	+ + +	+ + +	— — —	—	+ + +	+ + +

+ = hæmolysis.
— = no hæmolysis.

These experiments are confirmatory of and supplementary to those of Castellani already cited and furnish additional evidence of the nonidentity of syphilis and yaws.

A GENERAL DISCUSSION OF PELLAGRA[1] WITH REPORT OF A PROBABLE CASE IN THE PHILIPPINE ISLANDS.[2]

By DAVID G. WILLETS.

(From the Biological Laboratory, Bureau of Science, Manila, P. I.)

Pellagra is a chronic or acute, afebrile or febrile, endemic and at times epidemic, probably noncontagious, systemic disease of unknown etiology, occurring chiefly among the poorer classes of maize-eating peoples. It is characterized clinically by a seasonal periodicity, a typical skin eruption, digestive disorders and nervous and mental disturbances, and pathologically by slight peculiar anatomical lesions.

The disease first occurred in Spain in 1735, and now is found extensively in Italy and Roumania, in Greece, France, Austria, northern Portugal, Poland, Turkey, Africa, upper and lower Egypt, the West Indies, various parts of South America, Barbados, Mexico, and in the United States, especially in the South Atlantic portion. Two cases have been reported from England, several from India, one from Porto Rico, and two from the Panama Canal Zone. Although the cultivation of Indian corn and its consumption as food occurs in parts of the world from which pellagra is not reported, yet pellagra is unknown in sections where maize is not used as an article of diet.

The original home of Indian corn and the date of its introduction into Europe are apparently debatable questions, but nearly all authors agree that pellagra was not known in Europe until maize growing and eating had existed for some time. King(6) claims North America as the original home of Indian corn and also of pellagra and states that Baruino, in 1600, described meagerly a condition among certain Indian tribes which doubtless was pellagra and that he thought it arose from eating maize.

Gaspar Casal, in 1762, reported pellagra under the name of *mal de la rosa*, having seen his first case near Ovieda, Spain, in 1735, and subsequently other cases in the Asturias (Asturiensis). It was found in other parts of Spain within a few years, and in 1893, 2 per cent of the Spanish peasantry were pellagrous. (Tuczeh).[3]

The disease appeared in Italy, in the Lombardy district, in 1750, and gradually spread to other provinces. It was clearly described by Frapoli, of Milan, in 1771, under the name of pellagra (from *pellis*—skin, and *agra*—rough), and, according to King,(6) Frapoli declared it to be an ancient disease known in 1578 as pellarella, as might be seen by reference to the regulations for admission to the Hospital Major of Milan at that time. The ravages of the disease have been most marked in Italy and Roumania, where it appeared in 1810. In Italy, in 1879 there were 97,835 cases; in 1881, 104,067 cases; in 1899, 72,603, and in 1902, 55,029 (Wollenberg).(26) In Roumania, in 1885 there were 10,626 cases; in 1886, 19,797; in 1898, 21,272;(6) and in 1906, 30,000 cases (Triller).[4]

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[1] Synonymy: Mal de la Rosa; Mal de Padrone; Lepra Scorbutica; Asturiensis; Mal de Sole; Vernal insolation; Mal de Miseria; Maladie de la Teste; Buba tranjilar; Maidimus; Psychoneurosis Maidica.

[2] Read at a meeting of the Manila Medical Society, October, 1910.

[3] Quoted by Lavinder.

The elder Hameau[5] reported pellagra from the vicinity of Teste, France, in 1818 (*Maladie de la Teste*) and Pruner[6] found it in Africa in 1847. It appeared in Corfu, in 1856, and Sandwith found it in Egypt in 1893. Ray[7] reported it in 1892, from one of the provinces of North Bebar, India, and three physicians from India recognized photographs of cases of pellagra shown them by Sandwith in England as being typical of a condition they had seen in India, but had not understood. Two sporadic cases were reported in the United States in 1863 and 1864 by Doctor Gray, of Utica, New York, and Doctor Tyler, of Somerville, Massachusetts. Doctor Sherwell, of Chicago, found a case in a sailor on a ship in New York in 1902 and, in the same year, Dr. H. F. Harris,(4) of Atlanta, Georgia, reported a case of agchylostomiasis in a native of Georgia who had always resided in the State, presenting the typical symptoms of pellagra. In 1907, Searcy(17) described an epidemic of 88 cases in the Mount Vernon Hospital for the colored insane in Alabama. Since 1907 many articles relative to pellagra have appeared in American medical literature and many cases, especially from the insane institutions of the South Atlantic States, have been reported. The condition has become so serious in the United States that The National Association for the Study of Pellagra has been formed and the Surgeon-General of the Public Health and Marine-Hospital Service has appointed a commission to investigate the disease.

Since Marzari,[8] in 1810, associated pellagra with the eating of Indian corn, the majority of investigators of the disease have attributed it to the continued use of maize as a foodstuff; persons holding this opinion are known as the *zeists*, in contradistinction to the *antizeists* who consider the condition merely a symptom-complex occurring in alcoholics, insane persons, and in persons with other depressed symptoms (Lavinder).(7) However, the zeists differ widely in their beliefs as to just how the disease is caused by a diet of maize. Thayer(20) divides the opinions of this school into four classes, as follows: (1) Toxic substances are produced by changes occurring in healthy maize in the process of digestion (Neusser); (2) the poisons are chemical substances arising from the decomposition of maize before ingestion (Lombrosso); (3) the disease is caused by the products of changes produced [in maize] by various special micro-organisms and bacteria (Majocchi and Cuboñi); (4) it arises from changes produced [in maize] by various molds (Ballardini, Gosio and Ferrati, Ceni, Fossati).

Lavinder summarizes as follows the reasons why the ideas of the zeist school can not lightly be passed over:

"(1) The disease is an endemic one confined largely at least, if not exclusively, to populations which grow and eat corn and more especially to those who, through force of circumstances, eat a poor grade of corn. (2) By far the great majority of thinkers and students believe the disease to be in some definite, if at present rather ill-defined, way connected with the use of corn as a foodstuff. (3) Italian and other authorities, in their attempts to limit and eradicate pellagra, base all prophylactic measures almost entirely upon this theory and, as an outcome of such means, good results are claimed."

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[4] Quoted by King.
[5] Quoted by Lavinder.
[6] Quoted by Sambon.
[7] Quoted by King.
[8] Quoted by Taylor.

Sambon,(13) in 1905, referred to the United States as a conspicuous example of a maize-growing, maize-eating country which did not have pellagra, but, prior to June, 1909, Williams,(11) of South Carolina, obtained records of about 1,000 cases in that country, most of which were from asylums. It is variously estimated that at present there are from 5,000 to 10,000 pellagrins in the United States. Furthermore, it has been established that the disease doubtless existed there for at least fifteen or twenty years and probably for thirty-five or forty years before it was recognized. It is interesting in this connection to note certain changes in vogue in recent years regarding the harvesting and marketing of maize in the United States, as pointed out by Nichols(12): Shelled maize is marketed from four to eight weeks earlier than formerly, the time of weathering and drying it on the stalk also is cut short, and more trouble is experienced in handling the maize and preventing it from spoiling. Sambon,(13) in 1905, after discussing the various theories of the zeists as to the etiology of pellagra, concluded by saying that if he were asked to suggest a new theory of pellagra he would feel inclined to draw attention to the many analogies between it and some of the protozoan diseases. It has been claimed recently that the disease is caused by a protozoan(14) parasite transmitted to man by a minute biting midge of the genus *Simulium*. The protozoan theory is, at present, attracting much attention. Taylor(19) draws a striking comparison between the points of similarity occurring in pellagra, sleeping sickness and syphilis. However, the results secured by applying the Wassermann reaction to pellagrins are conflicting. Bass(1) obtained 8 positive reactions out of 12 cases, other conditions, such as syphilitic history, malaria, etc., which might have had their influence, being excluded. Fox,(3) on the other hand, obtained three or four weak reactions, but not a single strong positive one in 30 cases. However, he used Noguchi's modification of the Wassermann test.

The following conservative resolution was adopted at the closing session of the conference on pellagra, held at Columbia, South Carolina, November 3 to 4, 1909.

"*Resolved*, That while sound corn is in no way connected with pellagra, evidences of the relation between the use of spoiled corn and the prevalence of pellagra seem so apparent that we advise continued and systematic study of the subject and, in the meantime, we commend to corn growers the great importance of fully maturing corn on the stalk before cutting same."

Although individuals of all ages are susceptible to pellagra, the majority of cases occur in persons between 20 and 50 years of age. Locality predisposes only in so far as the climate may be favorable for the growing and maturing of corn. Other conditions have no predisposing influence except as the general state of nutrition may be lowered thereby. Direct sunlight is not necessary for the production of typical skin lesions of pellagra, though they may be influenced somewhat by it. Lombrosso, to some extent, controlled the location of lesions by the use of fenestrated gloves, but it is shown that gipsy children of Roumania, who go about naked, have skin lesions of pellagra confined to the usual sites (Neusser),[9] and five of Walker's(23) cases had not been out of doors in eight months.

The pathologic findings are neither constant nor characteristic, and Harris(5) says that "there are few, if any, diseases characterized by perceptible organic lesions the pathological anatomy of which is so difficult to arrive at as that of pellagra." The evidences of cachexia are seen in the wasted muscular tissue and in the atrophic and fatty changes in the heart, lungs, liver, kidneys, and spleen. In the digestive tract, the tongue is more or less denuded of epithelium, the gums and the buccal mucosa are the seat of a dirty, grayish deposit and perhaps of ulceration, the mucosa of the stomach is frequently hyperæmic, especially at the pyloric end, and slight areas of hyperæmia are found in various locations in the large and small intestine. Ulcerations also may occur and in various situations there usually is found a thinness of the walls of the intestine. When examined microscopically, this is found to be in the muscular tissue. In performing the autopsies, one is impressed with the slight pathologic changes in the digestive tract as compared with the marked symptoms which often precede death.

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[9] Quoted by Sambon.

Tuczeh[10] calls attention to abnormal pigmentation in the ganglionic cells, heart musculature, hepatic cells and spleen. He believes that the hyperæmia, anæmia, œdema and, at times, inflammatory affections of the central nervous system and its coverings, together with the obliteration of the central canal of the spinal cord, are not peculiar to pellagra, but are present in many chronic affections of the central nervous system and in senility. Other findings in the brain are negative, except for fatty degeneration or calcification of the intima of small blood vessels and pigmentation in the adventitial coats. However, in the cord, Tuczeh[11] found fairly constant and important changes, namely, a degeneration in the lateral columns in the dorsal region and in the posterior columns in the cervical and dorsal regions, with very few changes in the lumbar region. Lombrosso[12] confirmed these findings, as did Sandwith,(16) but they believed the lesions of the posterior columns to have originated in the posterior nerve roots. Harris(5) found a combined sclerosis and from the character of the lesions was led to discredit the occurrence of so-called acute pellagra, believing that practically all cases are chronic and die when suffering from an acute exacerbation.

The skin changes usually consist of congestion, thickening and pigmentation, and atrophic thinness. (Radcliffe-Crocker.)[13]

The alterations in the blood, other than a secondary anæmia, are inconstant. Relatively large mononuclear increase has been reported. In a few of Walker's(23) cases the hæmoglobin varied from 65 to 95 per cent, red cells from 2,500,000 to 5,292,000, whereas the white cells showed but slight and inconstant variations. Nucleated red blood cells were found in three out of ten cases and were present early in the disease and when the hæmoglobin was either normal or above that figure.

To sum up, aside from the changes in the skin and those to be expected in a general cachectic condition, practically the only constant pathologic findings are those in the spinal cord.

The attempt to discover prodromal symptoms has been unsatisfactory for the reason that the great majority of cases in Europe have occurred among the poorer agricultural classes, who are accustomed to pay but little attention to the lesser ills of life, as well as to the fact that most of the cases in the United States have been studied in insane institutions.

One of my cases, a white female, recovered sufficiently to give a fairly good history. The first symptoms which attracted her attention were slight vertigo, insomnia, an increased appetite, irritability, occipital headache, lassitude, a growing lack of interest in her home and family, slight irregularity in her bowel movements (chiefly of a diarrhœal nature), difficulty in remembering names, and a vague fear that some calamity would befall her. She did not recall having nausea, a burning sensation in the stomach, or abdominal pain particularly referred to the epigastric region, symptoms mentioned by various writers as prodromal of the disease.

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[10] Quoted by Lavinder.

[11] Quoted by Sandwith.

[12] Quoted by Sandwith.

[13] Quoted by Lavinder.

When pellagra is well established, the symptoms fall into three groups, skin lesions, digestive symptoms, and nervous and mental manifestations.

The skin lesions are symmetrical in distribution and involve chiefly, almost exclusively, the uncovered portions of the body: the hands, feet, face and neck. The elbows frequently are involved and lesions in unusual locations are reported: For instance, Walker had two cases in which the nipples were attacked and one case in which the umbilicus was affected. The extensor surfaces of the hands and feet are involved primarily; the palmar and plantar usually are not affected. The first appearance of the lesions generally is erythematous, but initial erythema may be lacking (Lavinder) (7). The erythema not infrequently is accompanied by some local puffiness and a sensation of burning, the whole picture being somewhat like sunburn. D'Oleggio believed the condition to be caused by the sunlight and as the lesions in Italy, at least, tend to recur in the springtime, he called it *vernal insolation,* the popular name being *mal de sole.*

Vesicles and bullæ which easily become infected may follow the erythema and these, upon breaking down, disclose a raw, weeping, and at times ulcerated surface. In other cases, the skin dries and desquamates, leaving a slightly pigmented surface, or possibly a normally appearing skin. However, initially the skin may be dry, rather thick and pigmented to a bronze or blackish color. As the attacks are repeated, a chronic thickening and an increase in the pigmentation occur in the affected parts. The majority of writers believe that there is no relation between the severity of the skin lesions and the constitutional disturbance, while others consider the moist variety of lesion to be a grave symptom.

In the digestive tract, stomatitis is present in a large percentage of cases. The edges and under surface of the tongue, the floor of the mouth and the inside of the cheeks usually are reddened and the tongue may later appear to have lost its epithelium, constituting the so-called "bald" tongue. A whitish pellicle frequently is present upon the lower gum and this may involve all the mucous membrane of the buccal cavity. Its first appearance not rarely is back of the last molar tooth. Abdominal distress, a burning sensation in the stomach, nausea and vomiting may be present. Diarrhœa is the rule, but there may be constipation. The diarrhœal stools are characteristically of a light yellow or greenish-yellow color, they have a very offensive odor and a decidedly acid reaction, are often of a mushy consistency and, as a rule, vary in frequency from 2 to 6 a day. When other symptoms are well marked and great emaciation is present, the diarrhœa at times may give place to constipation, a condition which the physicians at the Georgia State Sanitarium have learned to regard with apprehension.

The nervous symptoms are very variable, depending upon the stage of the disease and the individual case. The earliest symptoms are headache, restless irritability, insomnia (rarely drowsiness), vague neuralgias and some depression of spirits. As the disease advances, these symptoms become more marked and an alteration in the knee jerk occurs. In some cases, with mental symptoms similar to those of acute mania, all of the deep reflexes appear to be increased. Muscular weakness is characteristic. Many other conditions of a miscellaneous nature are reported, such as paraplegia, hemiplegia, contractures of the extremities, tetanoid states, convulsions, tremor of the tongue, head and upper extremities, and paræsthesias. Trophic changes also, such as œdema, sensations of cold, and general paleness, are reported.

Some cases show no mental involvement, while others vary from slow cerebration, faulty memory and slight depression, to asylum cases where almost any psychosis from dementia præcox to senility may be simulated. Some, with a history of long-continued illness, are diagnosed readily as an infective-exhaustive type, but others may be confused with manic-depressive insanity in the depressed stage, involutional melancholia, imbecility or dementia præcox. Negative symptoms, particularly with regard to taking food, not infrequently are present, and also stereotyped movements. Bizarre, fantastic, changeable delusions, often of the nature of a phobia, are at times coupled with a profound depression. As in the case of skin lesions, where a slight change is left in the affected parts when one attack clears up, just so some depression, irritability, and lack of interest in ordinary duties is left over, and as often as the disease recurs this condition is increased.

Many of the insane in Italy are pellagrins. There were 945 such cases in 1874, and 1,348 in 1877. Statistics for Saint Clement's Hospital of Venice give the following data (King) (6):

	Number of insane.	Pellagrous insane.
1874	558	178
1875	595	153
1876	666	175
1877	802	215
1878	859	294
1879	924	337

It is not stated whether these pellagrins were insane when admitted to the hospital or became pellagrous after admission.

A vaginitis is quite common in the genito-urinary tract, occurring about the same time as the skin lesions and the stomatitis. Coupled with these various symptoms there is an increasing emaciation as the pellagra recurs from year to year, until finally the patient dies of exhaustion or some intercurrent disease.

While nearly all of the old-world cases are of the chronic type just described, there are records of acute ones (Lavinder) (7). Walker (23) reports 51 cases of so-called acute pellagra in the United States; Searcy (17) 88 of epidemic acute pellagra, and Zeller (27), of Illinois, 130. Harris (5) is inclined to believe that all cases are chronic because of the nature of the pathologic lesions in the spinal cord, even of those who died in an apparently acute attack. In this connection it is interesting to note that Siler (18) found that many of the Illinois series gave a history of preceding attacks, whereas 80 per cent of Searcy's (17) were previously in good health. Certainly, there is a wide divergence clinically between the cases clearly chronic, recurring yearly, and those apparently acute, which, without giving a history of a preceding attack, terminate fatally in from about one week to two months.

The various symptoms of pellagra develop quickly and are severe in these rapidly fatal cases. The development of stomatitis, skin lesions, and digestive disorders in which vomiting is not uncommon and diarrhœa is persistent, leading to rapid emaciation, pronounced nervous and mental manifestations, vaginitis, slight fever and the occurrence of bedsores, is so rapid that the picture is rather explosive in character when compared with typically chronic cases which continue for years.

The division of pellagra into varieties depends upon the symptoms which are most pronounced. On this basis, the following division is given (Procopin):[14] (1) gastro-intestinal; (2) nervous, with mania; (3) nervous, with paralysis; (4) *pellagra sine pellagra;* and (5) typhoid pellagra.

Some authors discredit the occurrence of *pellagra sine pellagra,* and doubtless it is true that this division affords a good opportunity for other affections to be diagnosed as pellagra. There is no symptom more characteristic of pellagra than the skin lesions. However, I have seen at least one case in which the lesions were very slight and fleeting in character. In 8 per cent of Searcy's (17) series the cutaneous system was not involved. In the typhoid variety, a typhoid state has developed, but the *Bacillus typhosus* is absent.

The diagnosis of a well-marked case which exhibits the typical skin lesions, stomatitis, diarrhœa and depression is made easily after the physician has once seen pellagra. As in other affections, the atypical cases offer difficulties. A history of maize eating is important. In my opinion, the strongest evidence of pellagra is found in the skin lesions, and in the absence of this symptom one should be cautious in rendering a diagnosis. The London School of Tropical Medicine instructs its students to diagnose pellagra before the skin lesions appear, and certainly it would be well if diagnosis could be rendered thus early in all cases. However, as stated before, the division of *pellagra sine pellagra* affords an opportunity for incorrect conclusions to be drawn. Recently, I have read the reports of two or three cases of pellagra which, in my opinion, were not pellagra at all. Provisional diagnosis could be rendered in such instances and time would indicate the positive diagnosis.

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[14] Quoted by Lavinder.

The prognosis is guarded, even though the patient may recover from one attack. The most hopeful cases are those of the chronic type without mental involvement; the least so, those of the acute or fulminating variety with pronounced mental impairment. Searcy says that the majority of acute cases die within from ten days to six weeks after the onset. The chronic ones recur in increasing severity year after year and the patient finally dies of exhaustion, or of an intercurrent disease. Some affections are said to have continued for twenty-five years.

Fever, marked mental symptoms, and a typhoid state are looked upon with gravity, as also is any complication.

Lombrosso, in 1884, found that 13 per cent of a large number of cases died. (Lavinder.) The death rate in Italy in 1905 was 4 per cent.(26) Of the cases at the Peoria State Hospital, Illinois, 22 per cent died, 10 per cent were not expected to recover, 17 per cent improved, and 51 per cent apparently had recovered, when reported. (Siler.) (18)

Italy especially has instituted prophylactic measures against pellagra, all her efforts being directed against the use of spoiled maize as food. The Italian law of 1902 regarding the prevention and cure of pellagra provides for a census of the disease and a report of all new cases; artificial dessicating plants and public storehouses for maize; exchanges where, under certain conditions, good maize is given for spoiled; the exclusion from entrance into the country of spoiled grain and the inspection of home-grown maize when brought to the mill; the education of the public, including the school children, by means of lectures and pamphlets as to the causation and prevention of pellagra; and farmers' institutes to teach the peasantry better methods of agriculture. Apparently, the measures have been very successful, as indicated by the fact that in 1906, 1907, and 1908 the new cases reported were, respectively, 6,783, 5,307, and 2,766. (Wollenberg.) (26) However, it is pointed out that this decrease in the number of new cases is coincident with an improvement in general conditions in Italy; that emigration has reflexly widened the view of the peasant class so that they demand and get better food and living conditions; that wages are higher and that the consumption of meat is increasing. (Lavinder.) (9)

The law of 1902 provides, as curative measures, for the establishment of rural bakeries from which well-made, wheaten bread is distributed to those ill of pellagra, and also hospitals (*pellagrossari*) for the treatment of the more pronounced cases of the disease. There are now 22 such hospitals in Italy. (Thayer.) (20) The patients are given a liberal diet and are treated symptomatically, slight importance being placed on any one drug; and these efforts appear to be successful, since in 1906 and 1907 the death rate from pellagra in Italy fell to about one-fifth of the former death rate. (Wollenberg.) (26)

Austria, in 1905, provided for its pellagrins by establishing community bakeries where bread from fresh flour was distributed, each patient receiving daily a loaf weighing 1 kilo; salt and meat were given for a period of from sixteen to forty weeks; free pamphlets relating to the cause and prevention of the disease were circulated, with the result that 86 per cent of the patients were benefited to such an extent that they could attend to their ordinary duties even in cases where the disease was of from four to eight years' duration. In 1909 there were recurrences in 126 of the cases treated during 1907 and 1908. (Vienna letters.) (21, 22)

No drug has been found to counteract pellagra. The best results, as just indicated, have been obtained by excluding corn from the diet, giving a liberal allowance including meats, and treating the cases symptomatically. Tonics are often administered. The skin lesions do not respond well to local treatment. The exhibition of common salt is thought to be beneficial. Arsenic in the form of Fowler's solution, arsenic trioxide, atoxyl and soamin has been used, but reports of the results are very conflicting, some men apparently obtaining good results, while others believe that no beneficial effects are secured from its use. However, the balance of evidence tends to show that Fowler's solution is of importance, especially in nonasylum cases. Reports regarding the administration of atoxyl and arsenic trioxide combined have recently been made and encouraging results claimed (Babes),[15] but these have not been verified.

Bearing in mind that pellagra is a disease which characteristically recurs, it is evident that the physician must be exceedingly careful in interpreting apparently *good results* from the use of any drug. Warnock,[16] in 1907, believed atoxyl had a favorable action, but, in the following year, he lost faith in its beneficial effects (possibly because of recurrences).

There is evidence tending to show that specific antibodies are developed in the blood, and the serum of cured cases has been used successfully in the treatment of typhoid pellagra (Antonini and Mariani).[17] Cole and Winthrop (2) report successful results in 6 out of 9 cases treated by transfusion. In some of the cases the blood of a cured pellagrin was used, but in most of them the blood was taken from a healthy individual. Special reasons existed why the operation would probably be unsuccessful in the three which were fatal.

PELLAGRA IN THE PHILIPPINE ISLANDS.

Mariano Agustin, of Cabeceria No. 10, of San Antonio, a hacienda of the Compañia Tabacalera, and a barrio of Ilagan, Province of Isabela, an Ilocano, was born in Batac, Ilocos Norte. He moved to San Antonio about fifteen years ago. He is about 30 years of age and the father of three healthy children, the youngest of whom is between 3 and 4 years old. Since moving to San Antonio, he has continuously lived in that place and been engaged in growing tobacco. His family history is negative except that his father died suddenly two years ago at about 60 years of age. No history of serious illness could be elicited until the present illness began. The patient says his chief articles of diet have been maize, grown at San Antonio, and rice, but largely maize.

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[15] Quoted by Lavinder. [16] Quoted by Lavinder. [17] Quoted by Lavinder.

Somewhat more than two years ago the patient had attacks of diarrhœa alternating with constipation. The diarrhœal stools were of a mushy consistency, light yellow in color, and varied in number from two to six a day. About the time the diarrhœa developed, the skin of the extensor surfaces of the hands and feet became rather thick and pigmented, and the forearms, legs, thighs and buttocks were affected with a different kind of a dermatitis. Previously, his neck had become enlarged anteriorly. It was impossible to determine whether the hands and feet were reddened at first or whether the lesions were at any time moist.

While the patient says his hands and feet have been continuously pigmented since the eruption first appeared, his answers to certain questions tend to show that there have been three exacerbations or recurrences in his symptoms. He refuses to take a bath, except by having the water poured on his head, because his symptoms were more pronounced on one occasion after having taken a bath in the usual way; he also, for similar reasons, refuses to have his hair cut and his nails trimmed.

Throughout this period the patient has slept well and has had a good appetite, but has felt that he was growing weaker. In January, 1910, there were some skin lesions on his face. He realizes that he has become irritable and depressed. He has not walked for several months.

The patient is a fairly well nourished man of above medium height. His arms, and especially his legs, are diminished in size; the muscles are flabby. He complains of nothing but weakness. His countenance indicates mental depression, and this, together with his long hair and nails, a peculiar dermatitis involving the hands and feet symmetrically and an enlarged neck, probably from goiter, gives him a rather striking appearance.

A dry, rather thick, blackish, somewhat granular dermatitis involves the extensor surface of the hands quite symmetrically, and fades away rather abruptly slightly above the wrist joint; this gives place to a dermatitis which extends nearly to the elbow, involves the whole circumference of the forearm and is characterized by large, thin, grayish-colored flakes. At the wrist joint the first variety of determatitis spoken of extends around the forearms like a bracelet. The feet are affected in precisely the same manner as the hands and with precisely the same sort of dermatitis; it fades away rather gradually above the ankle joint to give rise to the large, flaky variety of dermatitis which involves not only the legs, but also the thighs and buttocks. This is more pronounced on the lower than on the upper extremities. Both varieties of dermatitis are symmetrical in distribution. The palmar and plantar surfaces are not involved. Slight puffiness of the extensor surfaces of the fingers is present. No burning sensation of the affected parts is experienced by the patient, but he complains of some itching wherever dermatitis is found.

Unfortunately, the patient's mouth was not examined, but he stated that his mouth was not at the time, and had not been, sore. Examination of the abdomen is negative, as is that of the lungs, but the heart is found to be enlarged, the apex beat being displaced outward and downward. No murmurs. The examination of the nervous system is unsatisfactory because it is impossible for the patient to understand what is desired. However, fine tremors of the upper extremities are present, the knee jerks appear to be diminished and the Babinski reflex is absent. Mentally, the patient is at times irritable and moody, but usually he is depressed and indifferent to what is going on around him. His answers to questions are slow, as though he had difficulty in finding words to express himself, and he apparently entertains vague fears that some ill will befall him. Memory for recent events is good. He has no hope of recovery. Pulse full, regular, 68 per minute. No capillary pulse, exophthalmos absent; temperature normal.

Facilities were not at hand for examining the blood or the urine, but the latter was apparently normal as to color, amount, and frequency. The fæces were light yellowish, soft, decidedly acid in reaction and negative for evidences of parasitism.

The patient was in about the same condition each time he was seen, and the above notes were taken from the results of examinations during five visits. He was told to abstain from eating maize and rice but that he might eat all he desired of other things, especially eggs, chickens and milk. He was also given elixir of iron, quinine and strychnine. The directions were not followed either as to diet or the tonic.

Having had the opportunity of seeing a number of cases of pellagra in the Georgia State Sanitarium during the past two years, I believe the case here reported to be one of that disease. The involvement of the hands and feet, the character of the bowel movements and the depression, cardinal symptoms of pellagra, all form a very striking picture. However, because of the impossibility of obtaining a perfectly accurate history either from the patient or his family, because of the presence of the second variety of dermatitis, which is new to me (but which is not uncommon at San Antonio), and because of the fact that pellagra has not yet been reported from the Philippine Islands, the diagnosis is modified to a case of probable pellagra.

It is well known that in certain parts of the Philippine Islands maize forms the chief article of diet. This is true of the tobacco districts of the Cagayan Valley, and among certain wild tribes (e. g., Negritos), in Bulacan and Pampanga Provinces. Since pellagra is found in so many parts of the world where maize is cultivated and used as a foodstuff, and it seems so apparent that the cause of pellagra is in some way connected with the eating of maize, one would rather expect to find the disease in the Philippine Islands. It may be added that several physicians have told me that certain cases seen by them may have been pellagrous. Dr. Cesar Sorerain, of Ilagan, tells me he has seen eight cases of pellagra during about twenty-two years of practice in the Cagayan Valley.

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